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Evidence for selection bias in influenza vaccine effectiveness studies: systematic review

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Background & Question

- **Evidence on influenza vaccine effectiveness (VE)**
  - is frequently derived from observational studies
  - is often used to support recommendations on influenza vaccination made by vaccination committees (ACIP, WHO-SAGE, STIKO)
- **However:**

→ **these studies are prone to bias, particularly selection bias, and have been suspected to overestimate VE if unspecific outcomes are used (e.g. mortality)**

Research questions

1) **How often do observational studies on influenza VE show indication of selection bias?**
2) **What is the impact on VE estimates?**
3) **How many of these studies show indication of residual confounding in the adjusted analyses?**

Forms of selection bias in vaccination studies:

- **Confounding by indication:** patients with underlying chronic diseases are more likely to be vaccinated

→ underestimation of VE

- **Healthy vaccinee bias:** patients who are in better health are more likely to be vaccinated

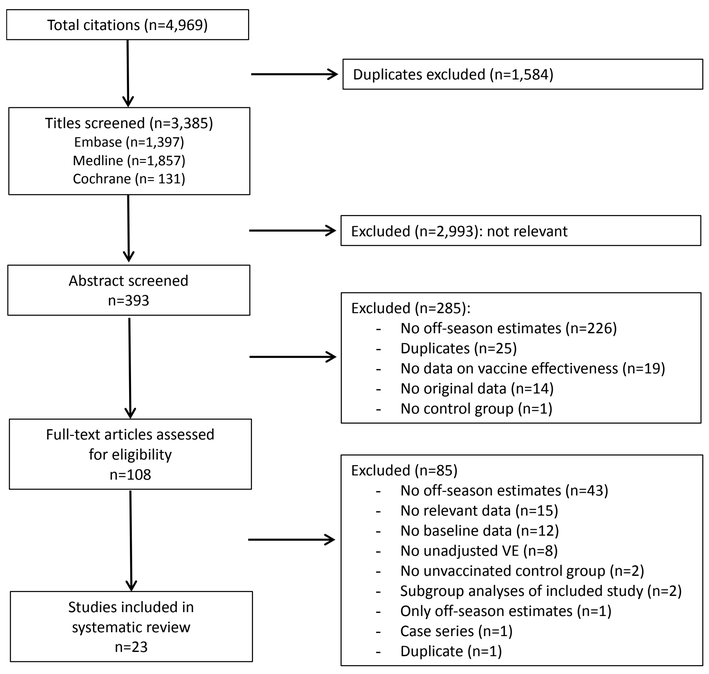
→ overestimation of VE

Methods

Systematic review:

- **Systematic searches** (Medline, Embase, Cochrane; last search: 25 May 2014)
- **Inclusion criteria**: i) observational study; ii) calculated influenza VE; iii) reported baseline characteristics; iv) reported crude and adjusted VE; v) investigated off-season VE
- **Assessment of risk of selection bias:** according to baseline characteristics (vacc. vs. unvacc.)
- **Comparison of unadjusted vs. confounder-adjusted VE estimates**
- **Comparison of season vs. off-season estimates**

Figure 1: Flow chart

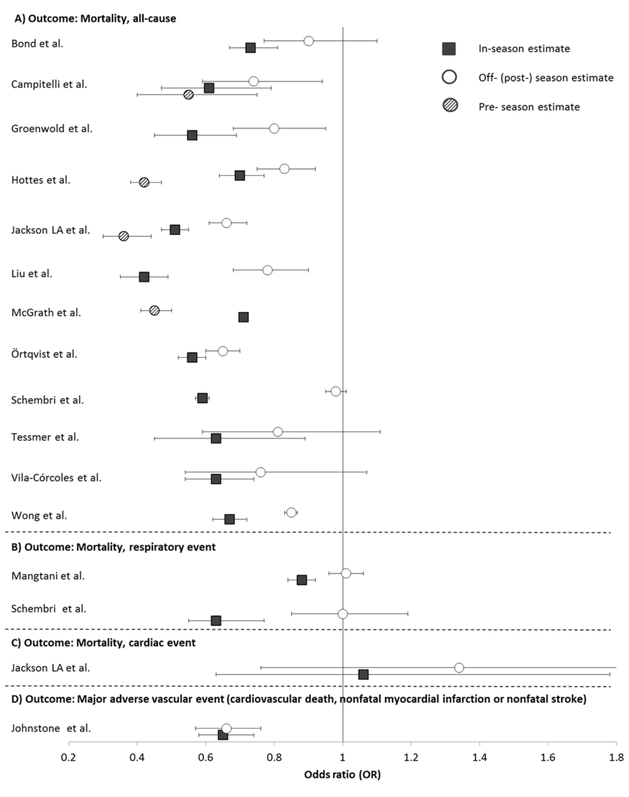


Concept of off-season VE estimates:

1) Outside the influenza season ("off-season"), the virus is (virtually) not circulating.
2) Therefore, no vaccine effect should be present.
3) Any VE measured during this control period is attributable to unmeasured confounding.
4) Off-season estimates have been suggested by some authors as an indicator for the presence of healthy vaccinee bias.

Results

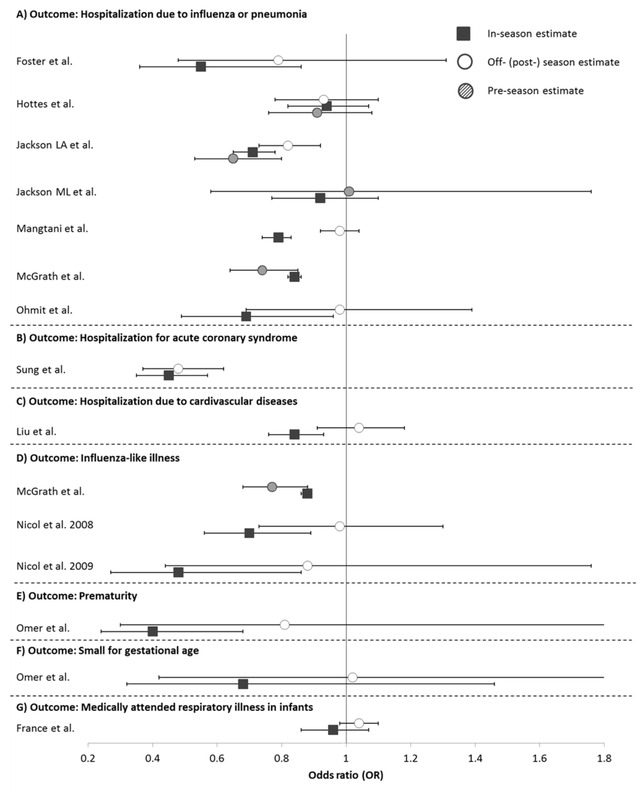
Figure 2: Season and off-season VE estimates (part 1)



Summary

- 23 studies identified (Fig. 1)
- reported on 11 outcomes (31 estimates)
- 19 studies = risk of selection bias
  - —14 studies = confounding by indication
  - —2 studies = healthy vaccinee bias
  - —3 studies = both forms of bias
- adjustment for confounders increased VE by 7 – 12%, depending on outcome
- 9 studies showed significant off-season VE estimates (Fig. 2+3)
- these occurred in 5 outcomes (all: unspecific, not lab-confirmed)

Figure 3: Season and off-season VE estimates (part 2)



Conclusions

- **Both forms of selection bias are likely to operate simultaneously in observational studies on influenza vaccine effectiveness.**
- **Although adjustment can correct for confounding by indication to some extent, the resulting estimates are still prone to healthy vaccinee bias.**
- **Cohort study designs using unspecific outcomes should no longer be used to assess influenza vaccine effectiveness.**
- **Instead, other study types, such as test-negative design or quasi-randomised studies with influenza-specific outcomes should be preferred.**

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